CLINICAL VIGNETTE

Hypercalcemia Preceding the Leukemic Transformation of Myelofibrosis

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Abstract

Malignancy is commonly associated with hypercalcemia, but myelofibrosis (MF) leading to hypercalcemia is quite rare and has not been previously well characterized. A 45-year-old woman with a history of essential thrombocytosis was found to have new pancytopenia. Her bone marrow biopsy noted tri-lineage hypercellularity and markedly increased reticulin fiber stain consistent with post-essential thrombocytosis myelofibrosis. Shortly after discontinuing her hydroxyurea, she was readmitted with bone pain and found to have hypercalcemia. There was no evidence of lytic bone lesions, PTH-rP secretion, hyperparathyroidism, or Vitamin D activation. The bone marrow did have increased numbers of active osteoclasts. Her serum calcium normalized after treatment with IV fluids, pamidronate and calcitonin. Shortly thereafter, her WBC rose to 22 with 2% circulating blasts, but repeat bone marrow biopsy and flow cytometry did not reveal increased blast morphology. Several months later, she presented to an outside hospital and a third bone marrow biopsy revealed leukemic transformation. Hypercalcemia from myelofibrosis has rarely been reported in the literature. The majority of cases of MF related hypercalcemia had bone pain or bone destruction, and the hypercalcemia resolved with osteoclast or mitotic inhibition. These cases demonstrate that the development of hypercalcemia in MF often heralds leukemic transformation, which portends a poor prognosis.

List of Abbreviations

Acute myeloid leukemia (AML), complete blood count (CBC), essential thrombocytosis (ET), hemoglobin (Hb), intact parathyroid hormone (iPTH), myelofibrosis (MF), parathyroid hormone-related peptide (PTHrP), thyroid stimulating hormone (TSH), white blood cell (WBC)

Background

Hypercalcemia may occur in up to 30% of patients with malignancy at some time during the course of their disease.[1-4] Myelofibrosis (MF) leading to hypercalcemia is quite uncommon, and has not been thoroughly characterized.[5-12]

Case Presentation

A 45-year-old female with past medical history of essential thrombocytosis (ET) was admitted to the hospital with nausea, vomiting, anorexia, and low back pain. She was diagnosed with ET 21 years prior to admission when she was worked up for abdominal and back pain and found to have portal vein, superior mesenteric vein, and splenic vein thromboses. Her platelet count at that time was 800 X 10^3/uL and a bone marrow biopsy showed increased megakaryocytes and reticulin excess. She was also found to have heterozygous protein C deficiency. Her clinical course was complicated by recurrent episodes of gastrointestinal bleeding due to portal gastropathy, and she required splenectomy and partial bowel resection as a consequence of her hypercoagulability. She had been on hydroxyurea and warfarin chronically.

Her admission complete blood count (CBC) revealed new pancytopenia with a white blood cell (WBC) count of 3.78 X 10^3/uL, hemoglobin (Hb) of 7.0 g/dL (mean corpuscular volume of 104.3 fL), and platelet count of 107 X 10^3/uL. She underwent bone marrow biopsy on hospital day 3, which revealed a hypercellular marrow with reduced multi-lineage maturation and increased megakaryocytes with clustering. Dysplastic megakaryocytes were evident with hypolobated forms and micromegakaryocytes. There were markedly increased reticulin fibers by reticulin (graded 4/4) and trichrome stains. Immunohistochemical staining showed that approximately 2% of cells expressed CD34, indicating no increase in myeloblasts. An elevated number of osteoclasts were also noted and confirmed with TRAP staining (Figure 1). Flow cytometry demonstrated that abnormal myeloblasts with aberrant expression of CD7 comprised 3.8% of total nucleated cells. Cytogenetics showed an aneuploid karyotype and very complex abnormalities in 11/20 metaphases. [43~45,XX,der(1)add(1)(p13)dic(1;11)(p13;q25),-5,t(6;17)(p11.2;p11.2), del(13)(q12q14),-18,+1~2mar]. Fluorescence in situ hybridization confirmed the -5 and +11q23 abnormalities. These results were consistent with high-risk post-ET myelofibrosis. Hydroxyurea was discontinued due to cytopenias and the patient was treated with supportive therapy including intravenous fluids, blood transfusion, and antiemetics and was discharged on hospital day 5.

Four days after discharge, the patient was readmitted with recurrence of her symptoms. She had numerous bouts of emesis and was experiencing postural dizziness. She also complained of constipation though she had had little oral intake since discharge. She denied taking a thiazide diuretic or calcium, vitamin D, vitamin A, and vitamin E supplements. Her vitals on admission were temperature 37.3C, heart rate 73, blood pressure 121/57, respiratory rate 20, and oxygen saturation 97%. Physical exam revealed a woman in generalized discomfort. The patient had pain on palpation of her lumbar spine and pelvis. She had 5/5 of strength in her upper and lower extremities and reflexes were 1+ at the biceps and patella bilaterally. Blood work on admission revealed a calcium level of 14.8 mg/dL (normal 8.7-10.5) with an ionized calcium of 2.09 mmol/L (normal 1.09-2.09), creatinine of 2.1 mg/dl (normal 0.5-1.3), lipase 52 U/L (normal 8-74) and alkaline phosphatase of 119 U/L (normal 31-103). Serum intact parathyroid hormone (iPTH) was 6 pg/mL (normal 11-51), 25-OH vitamin D was 22 ng/mL (normal 30-80), 1,25-OH vitamin D was 23 pg/mL (normal 15-75), PTH-related peptide was 0.7 pmol/L (normal <2), morning cortisol was 43 mcg/dl, thyroid stimulating hormone (TSH) was 5.9 mcIU/mL (normal 0.3-4.7), free T4 was 1.4 ng/dl (normal 0.8-1.6), serum and urine protein electrophoresis demonstrated no monoclonal spikes, and skeletal survey did not reveal any osteolytic or osteoblastic lesions.

The patient was treated with aggressive intravenous fluids, 1 dose of 60 mg intravenous pamidronate, and four doses of 200 units subcutaneous calcitonin. Serum calcium normalized on hospital day 3 and serum creatinine returned to baseline on hospital day 7. Her nausea, vomiting, abdominal pain resolved with normalization of her calcium. She required intravenous diuresis with furosemide after she developed volume overload from her fluid resuscitation. Throughout her hospitalization, she required escalating doses of opioids as she had bony pain in her back and bilateral lower extremities. She was discharged on hospital day 10.

The patient was readmitted again four days after discharge with increasing lethargy due to a urinary tract infection and opioid medications. The WBC was 22.8 with 2% circulating blasts on the peripheral blood smear. Given her persistent severe bone pain, a repeat bone marrow biopsy was performed to evaluate for leukemic transformation. Findings were similar to the most recent prior bone marrow biopsy, without evidence of increased blasts by morphology, flow cytometry, or immunohistochemistry. A marked reduction in osteoclasts was also noted compared to her previous biopsy weeks earlier (Figure 1). She was discharged on hospital day 12. Two weeks after discharge in follow-up clinic, the patient's calcium remained normal and her pain had stabilized.

Several months later, the patient was admitted to an outside hospital for altered mental status. Calcium levels were found to be as high as 13.4, and she was treated with pamidronate, calcitonin, and hydration. She was diagnosed with transformed acute myeloid leukemia after bone marrow biopsy. She underwent a matched unrelated donor stem cell transplant in along with a course of fludarabine and melphalan, but relapsed three months later and eventually succumbed to fungal and bacterial pneumonia complicated by status epilepticus.

Conclusions

This case of hypercalcemia presented classically with abdominal pain, nausea, and acute kidney injury, which resolved with treatment and normalization of her calcium levels. Malignancy is the most common cause of hypercalcemia in hospitalized patients, but MF leading to hypercalcemia is quite uncommon; only ten cases have been previously reported in the literature.[5-12,13]

Hypercalcemia associated with malignancy usually occurs through one of several common mechanisms, but the etiology of hypercalcemia in this case is less clear. MF has been reported to cause hypercalcemia through lytic bone lesions, parathyroid hormone-related peptide (PTHrP) secretion, 1, 25-DiOH Vitamin D activation, and RANK ligand.[5-12] Our patient had no evidence of lytic lesions, humoral hypercalcemia, Vitamin D activation, or PTHrP secretion. However, she did have diffuse bone pain and increased numbers of osteoclasts and hyperplastic bone marrow with 95% cellularity. Her hypercalcemia began after stopping her hydroxyurea and starting B12 and folate supplementation, which may have augmented her cell turnover and marrow expansion. Similarly, the hypercalcemia was controlled with inhibitors of mitosis in seven of the other ten cases (Table 1).[5,7-9, 12] Almost all of the cases (nine of eleven) had either bone pain or direct evidence of osteolysis, suggesting bone destruction is key to MF related hypercalcemia.[5-11] Four patients, including our own, were successfully treated with osteoclast inhibitors (Table 1).[5,10-11] Our patient had an increased number of osteoclasts on biopsy, which markedly resolved after bisphosphonate therapy. Similar hypercellular bone marrow with extensive expansion of osteoclasts was noted in another case report.[7] Together, this suggests the myelofibrotic cells within the bone marrow lead to osteoclast activation, destruction of bone trabeculae, and release of calcium into the circulation. This cascade can be controlled either by mitotic inhibitors or by directly inhibiting osteoclasts, the final common pathway.

The patient had a long history of ET that transformed to MF immediately before the onset of hypercalcemia. Seven of the other ten cases also went through cellular transformation around the onset of hypercalcemia.[5-7,10,12] This patient's clinical presentation of severe bone pain, cytopenias, and hypercalcemia was also concerning for transformation to acute myeloid leukemia (AML). Four of the case reports of MF associated hypercalcemia developed leukemic transformation.[5,7,10,12] Our patient had a repeat bone marrow biopsy, which did not yield any evidence of leukemia, but it should be noted two of the cases of MF-related hypercalcemia did not discover this leukemic transformation until the extramedullary foci were found on autopsy.[5,7]

Development of hypercalcemia in patients with malignancy is associated with an increased mortality.[14] The same appears be true for myelofibrosis associated hypercalcemia. Seven of the eleven reported cases died within six months, most within one month.[5-7,10-12] The patient's unfavorable cytogenetics also suggested a poor prognosis.[15]

Malignancy is commonly associated with hypercalcemia, but it is rarely seen with MF. A review of the few cases of MF-related

hypercalcemia suggests a common pathway of osteoclast activation and subsequent osteolysis. Successful treatments have included mitotic inhibitors and osteoclast inhibition. These cases also reveal that the development of hypercalcemia in MF can herald leukemic transformation, which portends a poor prognosis.

Figures and Tables

Figure 1. Bone marrow biopsies. A: H&E stain showing osteoclasts (arrows) before bisphosphonate administration. B: TRAP stain for osteoclasts (arrows) before bisphosphonate administration. C: H&E stain showing the disappearance of osteoclasts after bisphosphonate administration. D: TRAP stain showing the disappearance of osteoclasts after bisphosphonate administration.

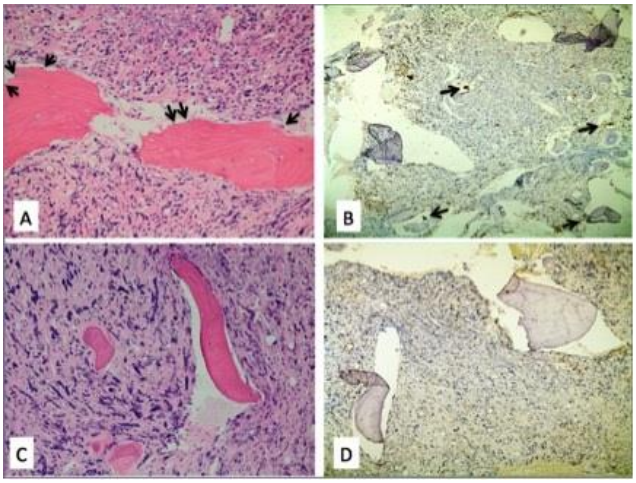

Table 1. Factors associated with hypercalcemia in MF

Factor	Cases (referred to by reference #)	Incidence
Presence of bone pain	6, 8-1, 8-2, 9, 10, current	55% (6/11)
Presence of bone pathology[a]	5, 6, 7, 10, 11, current	55% (6/11)
Presence of cellular transformation	5, 6, 7, 10, 11, 12-1, 12-2, current	64% (7/11)
Successfully controlled by mitotic inhibitors	5, 7, 8-1, 8-2, 9, 12-1, 12-2, current	73% (8/11)
Successfully treated by osteoclast inhibitors	5, 10, 11, current	36% (4/11)

[a]Lytic bone lesions in cases 5, 6, 11, and current. Increased osteoclasts in cases 7 and current. Increased serum markers of osteolysis in case 11.

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